Immune correlates and long-term follow-up of a Phase Ia study of MPDL3280A, an engineered PD-L1 antibody, in patients with metastatic renal cell carcinoma (mRCC)

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Disclosures

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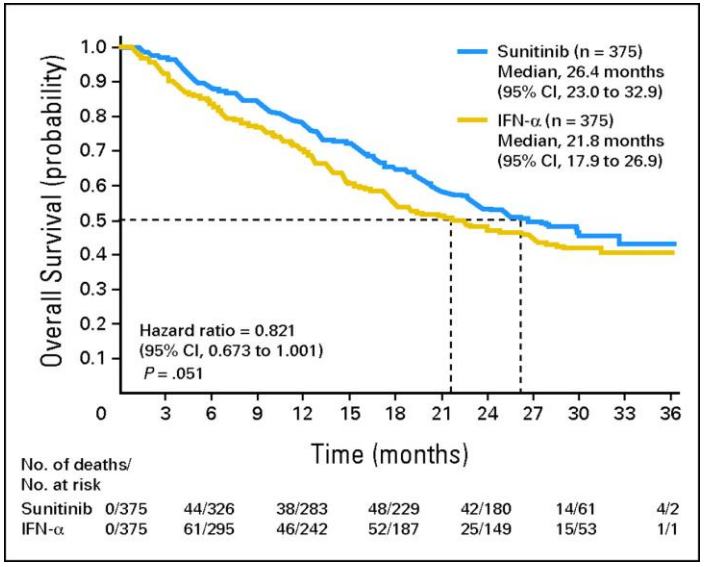
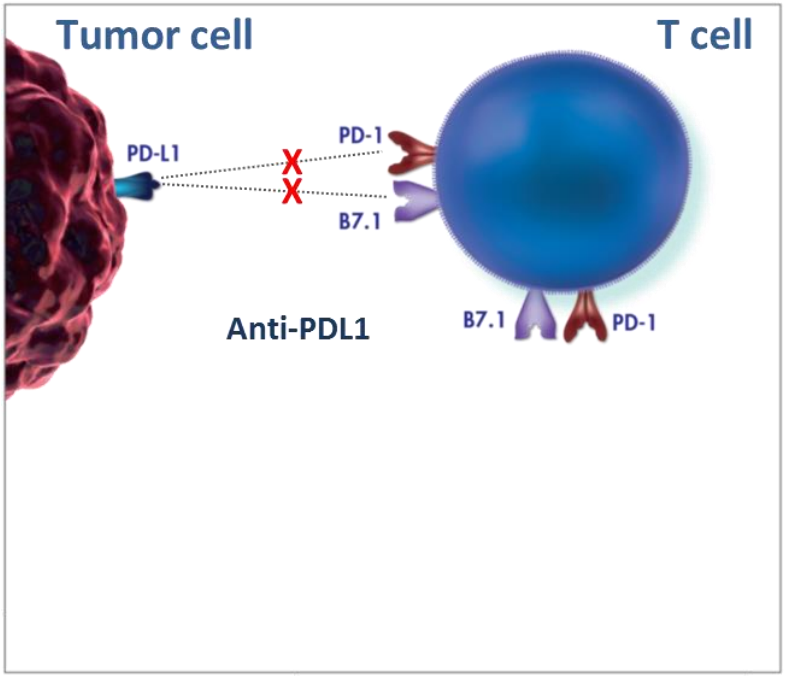
Metastatic Renal Cell Carcinoma (mRCC)

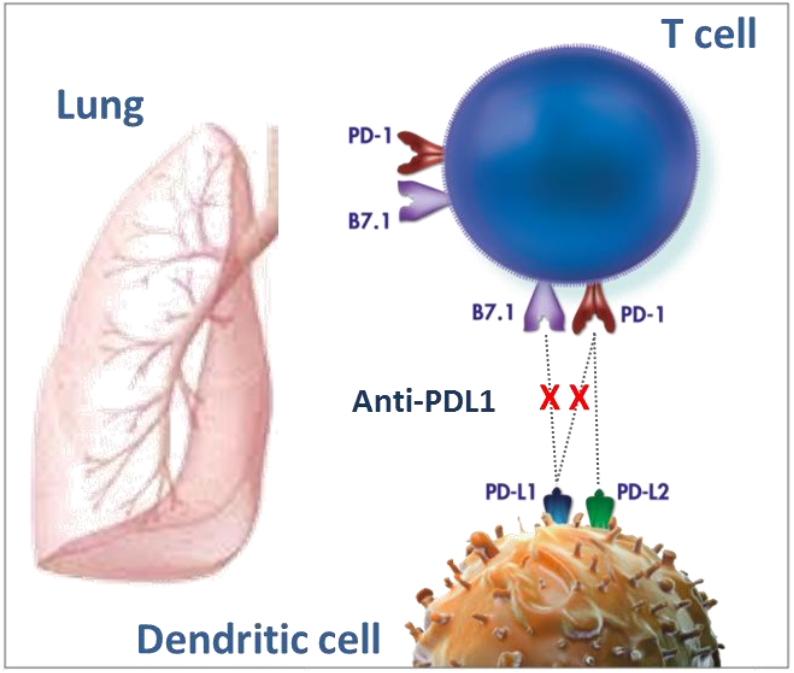
- The median OS for treatment-naive patients with mRCC is approximately 2 years[1,2]
- VEGF TKIs are the standard of care for clear cell mRCC but are associated with chronic toxicity (e.g., fatigue, diarrhea, HFS, etc.) and acquired resistance[3]
- A high unmet need exists for agents that induce a high proportion of durable tumor responses with acceptable toxicity for patients with mRCC[3]



1. Motzer. *J Clin Oncol.* 2014. 2. Sternberg. *Eur J Cancer*. 2013. 3. Bracarda. *Eur Urol*. 2009.

MPDL3280A is an Engineered Anti-PD-L1 Antibody That Inhibits the Binding of PD-L1 to PD-1 and B7.1

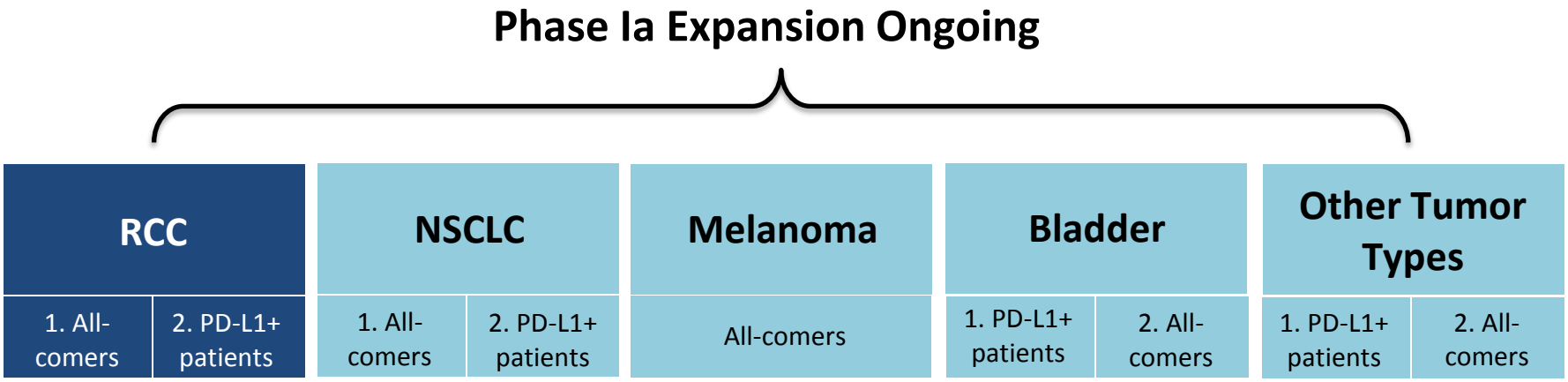




- Inhibiting PD-L1/PD-1 and PD-L1/B7.1 interactions can restore antitumor T-cell activity and enhance T-cell priming
- MPDL3280A leaves the PD-L2/PD-1 interaction intact, maintaining immune homeostasis and potentially preventing autoimmunity

1. Akbari. *Mucosal Immunol.* 2010; 2. Matsumoto. *Biochem Biophys Res Commun.* 2008.

MPDL3280A Phase Ia



MPDL3280A administered by IV q3w for up to 16 cycles

Key Eligibility Criteria

Measurable disease per RECIST v1.1

ECOG PS 0 or 1

- First RCC patient was enrolled on Dec 12, 2011. Last RCC patient was enrolled on Jul 18, 2013

MPDL3280A: mRCC Baseline Characteristics

Safety-evaluable population with RCC in Phase I expansion

Characteristics	All Patients, N = 69
Median age (range), y	61 (33-81)
Male	77%
ECOG PS 0 / 1	54% / 46%
Histologic subtypes, n (%)	
Clear cell	62 (90%)
Non–clear cell	7 (10%)
Fuhrman grade 4 or with sarcomatoid histology	20 (29%)
MSKCC poor risk, n (%)	18 (26%)
Prior nephrectomy, n (%)	66 (96%)
Previous systemic therapies, n (%)	60 (87%)
Cytokine-based	27 (39%)
Tyrosine kinase inhibitor	40 (58%)
mTOR inhibitor	17 (25%)
Lung/liver/bone/brain metastases at enrollment, n (%)	49 (71%) / 16 (23%) / 24 (35%) / 3 (4%)

Clinical data cutoff Apr 21, 2014; MSKCC, Memorial Sloan Kettering Cancer Center.

MPDL3280A: Treatment-Related Adverse Events

Safety-evaluable population with RCC in Phase I expansion

- Median duration of treatment was 239 days (range, 21-834 days)
- 80% of patients experienced a treatment-related AE
- Treatment-related Grade 3 AEs occurred in 11 patients (16%), including anemia (4%), dehydration (3%), fatigue (3%) and hypophosphatemia (3%)
- No treatment-related Grade 4 AEs or deaths were reported

Patients With RCC, N = 69 (Data cutoff Apr 21, 2014)	All Grade[a] n (%)	Grade 3-4 n (%)
Fatigue	15 (22%)	2 (3%)
Decreased appetite	11 (16%)	0
Arthralgia	10 (15%)	0
Rash	10 (15%)	0
Diarrhea	8 (12%)	0
Pruritus	8 (12%)	0
Pyrexia	8 (12%)	0
Chills	7 (10%)	0
Nausea	7 (10%)	0

[a] Includes all-grade events occurring in ≥ 7patients (10%).

MPDL3280A: Efficacy by PD-L1 IHC (IC)

Efficacy-evaluable population with clear cell RCC

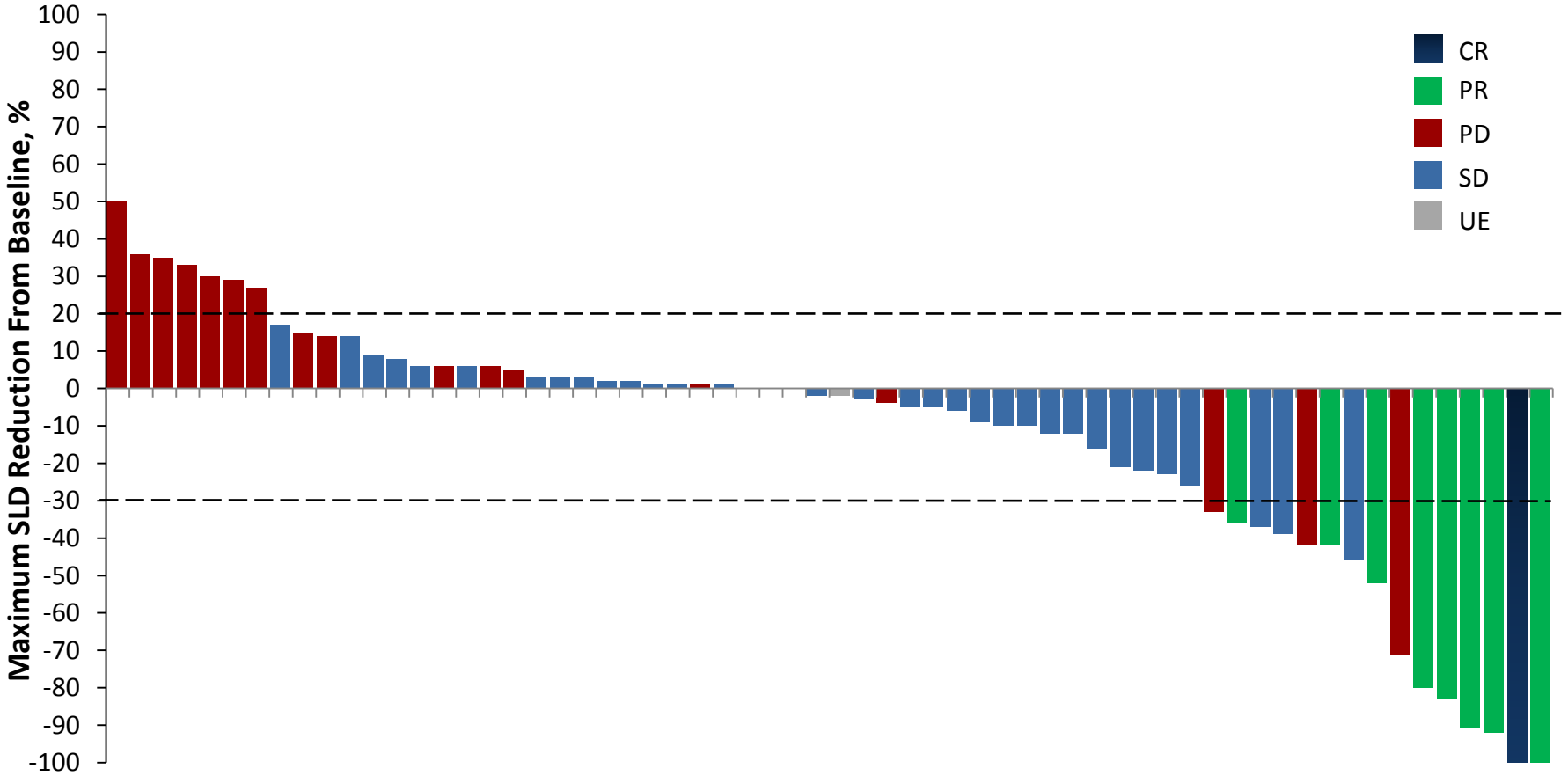
PD-L1 IHC - tumor-infiltrating immune cells (IC)[a], n = 62	ORR (95% CI), %
Overall	15% (8-25)
IHC (IC) 1/2/3	20% (9-37)
IHC (IC) 0	10% (2-30)

- 24-week PFS rate was 51% (95% CI: 38-63)
- 1 CR (IHC [IC] 3)
- ORR for Fuhrman grade 4 or sarcomatoid clear cell RCC (n = 18) was 22% (95% CI: 8, 47)

[a] A PD-L1+ cohort of patients was enrolled. 6 patients had unknown PD-L1 IHC (IC) status.
Investigator-assessed confirmed ORRs per RECIST v1.1.
Patients dosed by Oct 21, 2013; data cutoff Apr 21, 2014.
IHC 3: ≥ 10% of ICs are PD-L1+; IHC 2: ≥ 5% but < 10% of ICs are PD-L1+; IHC 1: ≥ 1 % but < 5% of ICs are PD-L1+; IHC 0: < 1% are PD-L1+.

MPDL3280A: Summary of ORR in Clear Cell RCC

Efficacy-evaluable population with clear cell RCC in Phase I expansion



- Median duration of follow-up was 9 months (range, 1-27 months)

Patients dosed by Oct 21, 2013; data cutoff Apr 21, 2014. Investigator-assessed confirmed ORRs per RECIST v1.1.
CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease; UE, unable to evaluate.

McDermott et al., 26-30 September 2014, Madrid, Spain

MPDL3280A: Efficacy by MSKCC Prognostic Group

Efficacy-evaluable population with clear cell RCC

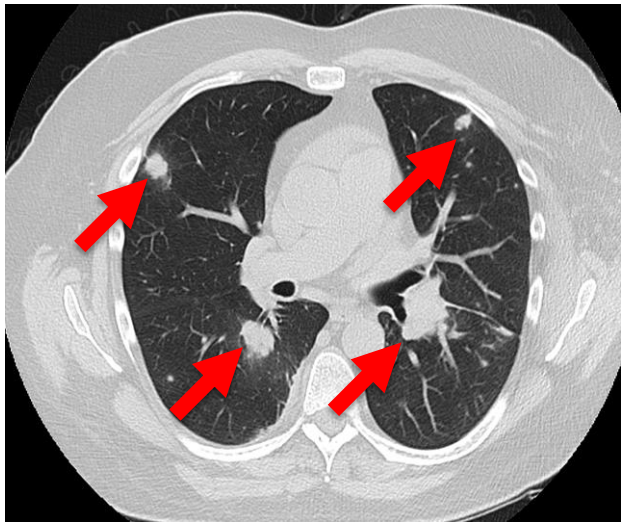
Risk Category	All patients		IHC (IC) 1/2/3[a]	
	n	ORR, n (%) 95% CI	n	ORR, n (%) 95% CI
Overall	62	9 (15%) CI: 8-25 **1 CR and 8 PRs**	35	7 (20%) CI: 9-37 **1 CR and 6 PRs**
Favorable	10	2 (20%) CI: 4-56	3	0 CI: 0-63
Intermediate	36	3 (8%) CI: 2-21	24	3 (13%) CI: 4-31
Poor	15	4 (27%) CI: 10-55	7	4 (57%) CI: 23-87

- Higher response rate observed in MSKCC poor-risk patients with PD-L1 IHC (IC) 1/2/3 expression

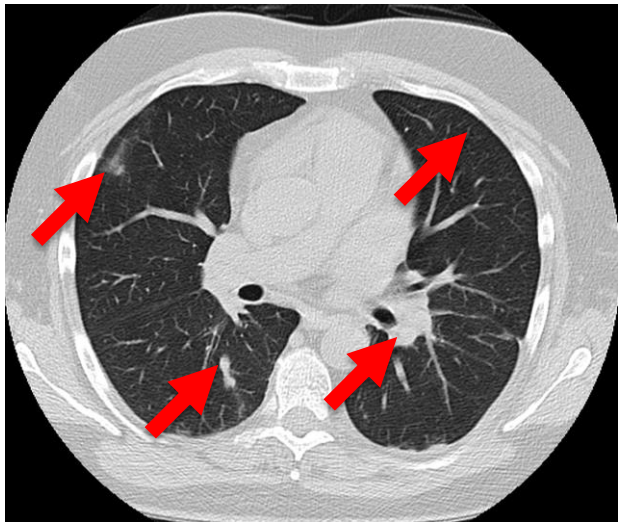
[a] 1 patient had unknown PD-L1 IHC (IC) status.
MSKCC, Memorial Sloan Kettering Cancer Center.
Investigator-assessed confirmed ORRs per RECIST v1.1. Patients dosed by Oct 21, 2013; data cutoff Apr 21, 2014.
IHC 3: ≥ 10% of ICs are PD-L1+; IHC 2: ≥ 5% but < 10% of ICs are PD-L1+. IHC 1: ≥ 1 % but < 5% of ICs are PD-L1+; IHC 0: < 1% of ICs are PD-L1+.

MPDL3280A: Response in Patient With Sarcomatoid Variant mRCC

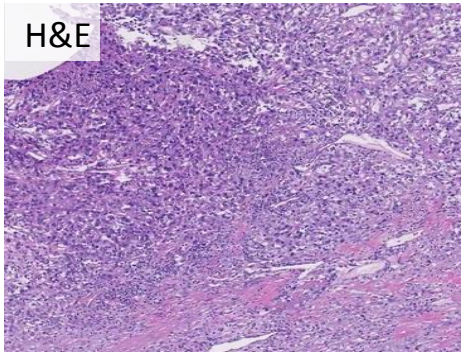
Pre-treatment (9 Mar 2012)

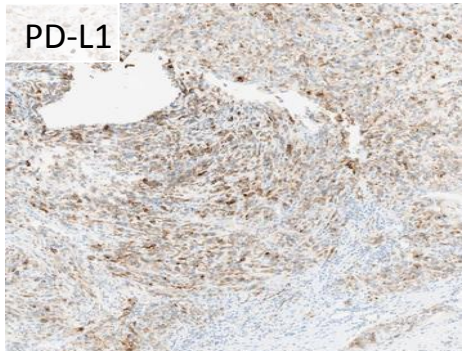


Post–cycle 2 (20 Apr 2012)



Pre-treatment tumor specimen





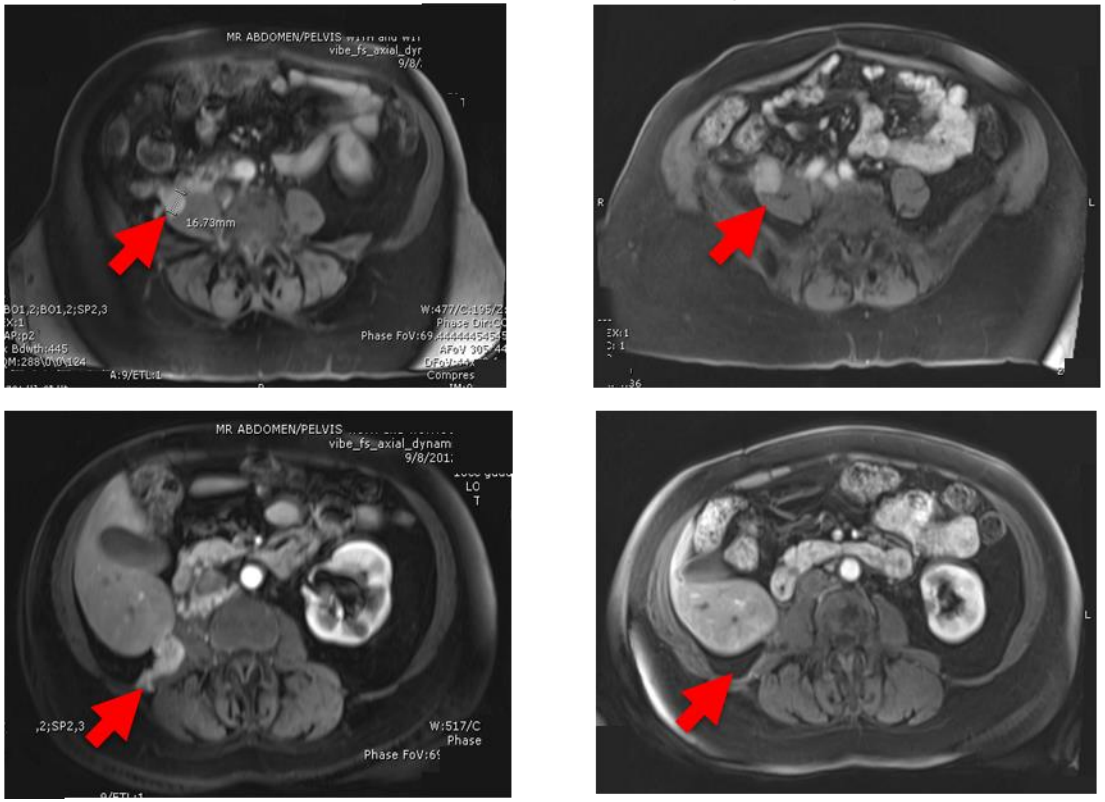
- 51-year-old man with metastatic RCC (75% sarcomatoid variant) diagnosed Oct 2011 with T3aN2 disease, s/p L nephrectomy; now metastatic to lungs, skin and bone
  - Prior sunitinib, temsirolimus and XRT to T9
- Poor MSKCC risk and ECOG PS 1
- PD-L1 IHC (IC) positive (IHC 3)
- Duration of response was 76 weeks

Carolina BioOncology Institute (Powderly).

MPDL3280A: irRC Partial Response in Patient With Metastatic Oncocytic Papillary RCC

Pre-treatment (8 Sept 2012)

Post–cycle 8 (26 Feb 2013)



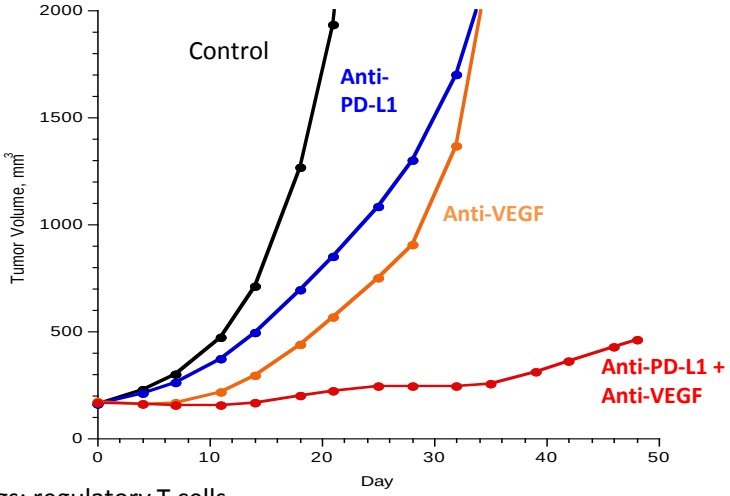
- 72-year-old woman with metastatic RCC oncocytic papillary RCC s/p R nephrectomy and sunitinib
- PD-L1 IHC (IC) negative (IHC 0)

irRC, immune-related response criteria.
Yale School of Medicine (Sznol/Herbst).

Rationale to Combine MPDL3280A With Bevacizumab

- Single agent bevacizumab (10 mg/kg) has demonstrated a 10% ORR [95% CI: 2.9, 24.2] in RCC[1]
- Anti-VEGF therapy has immunomodulatory properties
  - Increases trafficking of T cells into tumors[2,3]
  - Reduces suppressive cytokines and infiltrating Tregs and MDSCs[4,5]

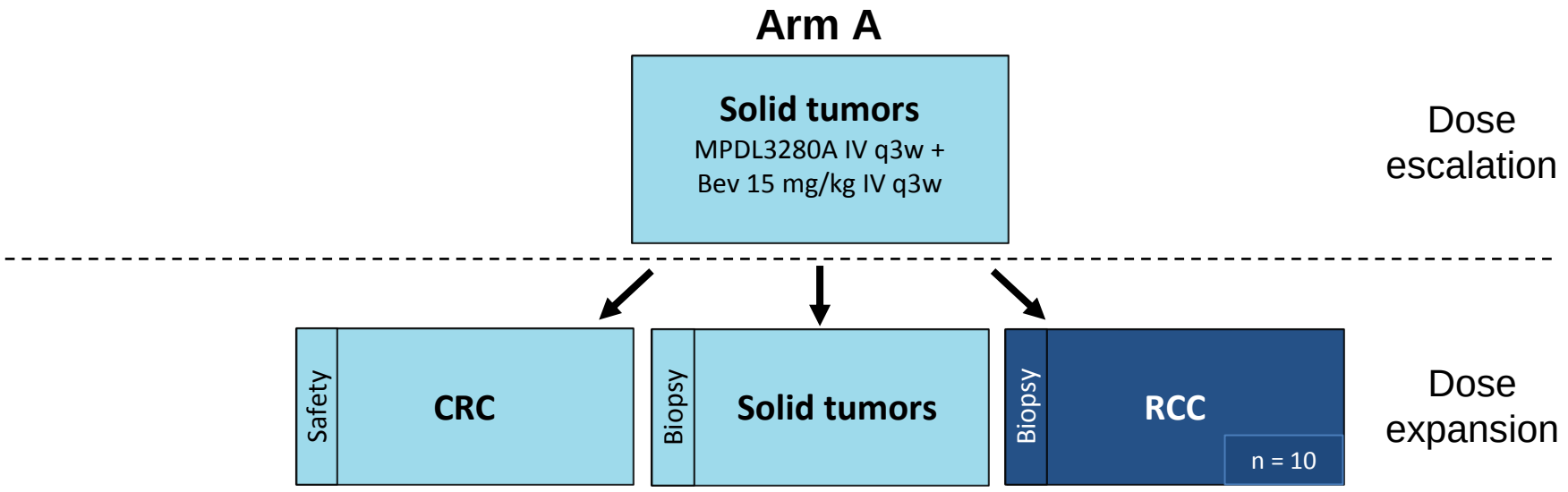
Cloudman melanoma model[6]



MDSC, myeloid-derived suppressor cell; Tregs; regulatory T cells .

1. Yang. *NEJM*. 2003. 2. Manning. *Clin Cancer Res.* 2007. 3. Shrimali. *Cancer Res.* 2010. 4. Kutsmartsev. *J Immunol.* 2008. 5. Roland. *PLOS One.* 2009. 6. Genentech, data on file.

MPDL3280A + Bevacizumab: Phase Ib Study Design Arm A[a]



- Primary objectives: safety, tolerability, DLT and MTD
- Secondary objectives: preliminary anti-tumor activity and PK

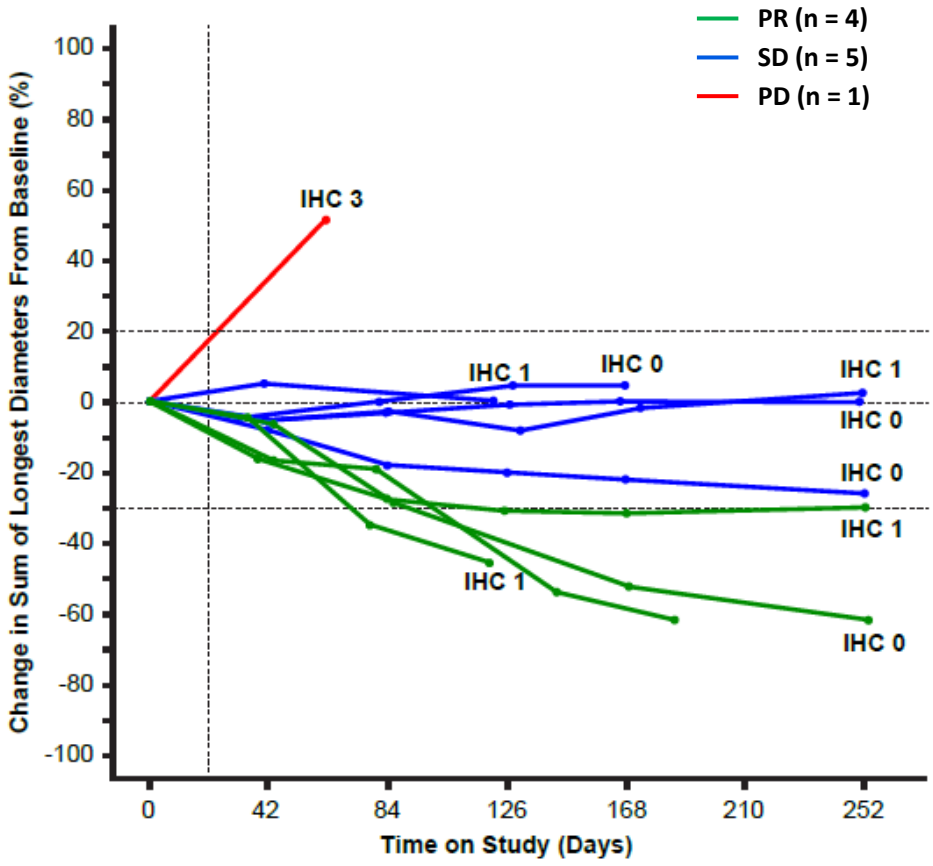
[a] Lieu et al., abstract 1049O, presented Saturday.

MPDL3280A + Bevacizumab: Summary of Phase Ib Results

Safety and efficacy of patients in Arm A[a]

- Safety
  - All patients in Arm A (n = 35) experienced an AE, with 49% experiencing a G3-4 AE, regardless of attribution
  - 1 MPDL3280A-related Grade 3 AE occurred (1 case of neutropenia in Arm A)
  - No Grade 4 AEs or deaths were attributed to MPDL3280A

- Efficacy in patients with 1L clear cell RCC
  - 4 of 10 patients demonstrated an objective response
  - 5 of 10 patients experienced stable disease
  - Responding patients included 2 with IHC (IC) 1, 1 with IHC (IC) 0 and 1 with IHC (IC) unknown



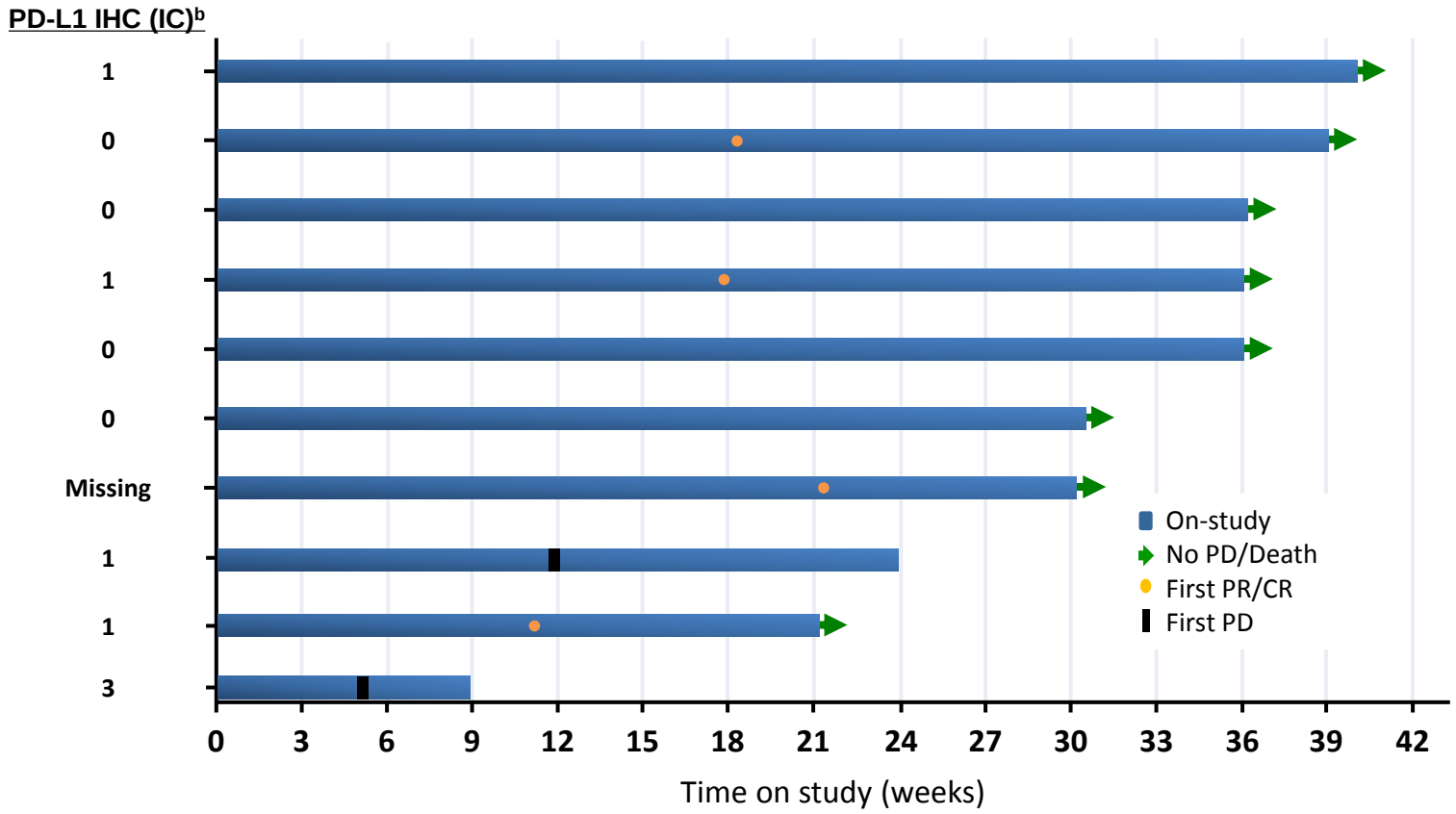
[a] Lieu et al., abstract 1049O, presented Saturday.

Patients dosed by Apr 7, 2014; data cutoff Jul 7, 2014; Unconfirmed best responses by RECIST v1.1.

IHC 3: ≥ 10% of ICs are PD-L1+; IHC 2: ≥ 5% and < 10% of ICs are PD-L1+. IHC 1: ≥ 1% and < 5% of ICs are PD-L1+; IHC 0: < 1% ICs are PD-L1+.

MPDL3280A + Bevacizumab: Duration of Treatment and Response in 1L RCC

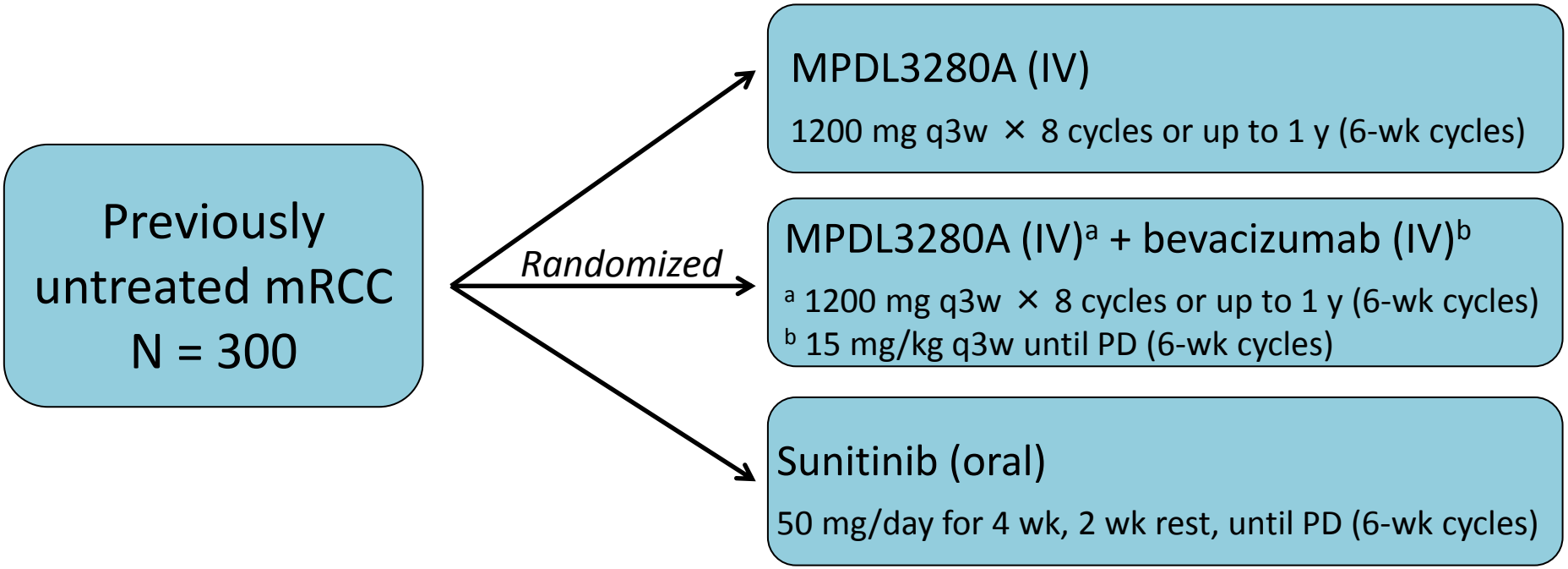
Efficacy-evaluable population with 1L clear cell RCC in Arm A[a]



- SD ≥ 24 weeks in 4 patients
- 9 of 10 patients with mRCC remain on study treatment

[a] Lieu et al., abstract 1049O, presented Saturday.
Patients dosed by Apr 7, 2014 who had at least 1 scan; data cutoff Jul 7, 2014.
[b] IHC 3: ≥ 10% of ICs are PD-L1+; IHC 2: ≥ 5% and < 10% of ICs are PD-L1+. IHC 1: ≥ 1% and < 5% of ICs are PD-L1+; IHC 0: < 1% ICs are PD-L1+.

Study WO29074 MPDL3280A: Phase II Trial in mRCC (NCT01984242)



- Key objectives: evaluate efficacy of sunitinib vs MPDL3280A as monotherapy or in combination with bevacizumab
- Primary endpoint: PFS per RECIST v1.1
- Crossover allowed

MPDL3280A: Conclusions

- MPDL3280A was well tolerated
  - Both as a single agent and in combination with bevacizumab
- MPDL3280A demonstrated promising efficacy in previously treated clear cell mRCC
  - Median PFS = 24 weeks (range, 5-98+ weeks)
  - ORR = 22% for Fuhrman grade 4 or sarcomatoid clear cell mRCC
- Preliminary data indicated that MPDL3280A had better efficacy in patients with PD-L1 expressed on tumor-infiltrating immune cells
- MPDL3280A demonstrated clinical activity in combination with bevacizumab in 1L clear cell mRCC
  - ORR = 40%; SD = 50%

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The patients and their families

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Carolina BioOncology (Powderly)
Centre Léon-Bérard (Cassier)
Comprehensive Cancer Centers of Nevada (Braiteh)
Dana-Farber Cancer Institute (Hodi)
Gustave Roussy (Bahleda, Hollebecque)
Johns Hopkins (Drake, Emens)
Massachusetts General Hospital (Lawrence, Lee)
Moffitt Cancer Center (Antonia, Zhang)
New York Oncology Hematology (Garbo)
Sarah-Cannon Research Institute (Burris)
Stanford University (Kohrt, Srinivas)
Vall d'Hebron University Hospital (Tabernero)
Virginia Oncology Associates, US Oncology (Conkling)
Yale School of Medicine (Herbst)